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DATA EVALUATION REPORT

STUDY TYPE: Metabolism in Rats TOX CHEM NO. 838B

MRID NO. 401611-07

TEST MATERIAL: Unlabeled, ^{14}C acid labeled and ^{14}C alcohol labeled---2,3,5,6-tetrafluoro-4-methylbenzyl-cis-3-(Z-2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropane carboxylate

SYNONYMS: Tefluthrin, PP993

STUDY NUMBER: UR0163, UR0167,

SPONSOR: Imperial Chemical Industries PLC

TESTING FACILITY: ICI Central Toxicology Laboratory

TITLE OF REPORT: PP993: Absorption, Excretion and Tissue Distribution of a Single Oral Dose (1 mg/kg) in the Rat

AUTHOR(S): M. Prout, E. Howard, A. Soames

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CONCLUSIONS:

The major proportion (75-85%) of a single oral dose (1 mg/kg) of ^{14}C PP993 (acid and alcohol labeled) was excreted in feces and urine within 48 hrs. of administration. Depending on the sex of the rat and the position of the label, mean levels of 20-33% of the given dose were measured in urine during the 7-day observation period, therefore, at a minimum, the proportions of the dose measured in urine were absorbed. Whole body autoradiography assays on 1 rat/sex showed that the density of the labeled compound was greatest in the gastrointestinal tract, but was also detectable in liver and, to a lesser extent, in kidney. Tissue retention assays verified the presence of residual radioactivity in liver and kidney, however, the levels were typically less than 1.0 and 0.02%, respectively, of the administered dose.

Core Classification: Collectively with 2 other metabolism studies (MRID NOS.: 401611-08 and 401611-11) submitted concurrently: minimum

Quality Assurance: A signed statement was submitted with the study.

Materials

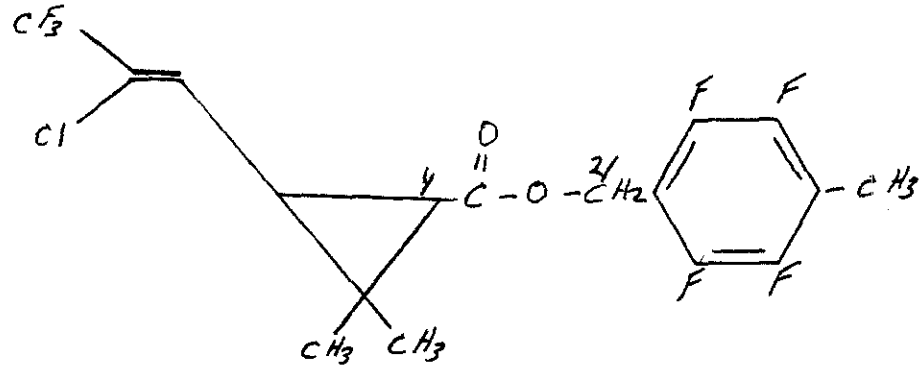
Unlabeled test substance: 2,3,5,6-tetrafluoro-4-methylbenzyl-cis-3-(Z-2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropane carboxylate (PP993); purity= 99.1%.

Labeled test substance:
a/ ^{14}C acid labeled PP993; labeled in the cyclopropane ring; specific activity= 2.3 GBq/mmole; radiochemical purity= 97%.

b/ ^{14}C alcohol labeled PP993, labeled in the methylene group; specific activity= 2.1 GBq/mmole; radiochemical purity= 97%.

Supplier

Both labeled and unlabeled compounds were provided by Imperial Chemical Industries PLC.



Position of radiolabel
1/ ^{14}C acid labeled PP993
2/ ^{14}C alchohol labeled PP993

Dosing solutions

The dosing solutions were prepared by the admixture of unlabeled and radiolabeled PP993 in corn oil to provide:

a/ Dosing solution 1: 0.26 mg/ml cold PP993 and 2.2 MBq/ml acid labeled PP993.
b/ Dosing solution 2: 0.33 mg/ml cold PP993 and 2.2 MBq/ml alcohol labeled PP993.
c/ Dosing solution 3: 0.25 mg/ml cold PP993 and 5 MBq/ml alcohol labeled PP993.

Animals

Male and female rats (170-250 g) of the Alpk/AP strain

Methods

Dosing (via oral intubation)

a/ First experiment: 4 rats/sex received a single dose of ^{14}C acid labeled PP993(4.0 ml/kg of Dosing solution 1.

b/ Second experiment: 4 rats/sex received a single dose of ^{14}C alcohol labeled PP993 (3.3 ml/kg of Dosing solution 2)

The dosage level of PP993 in both experiments was 1 mg/kg.

Excretion Balance Experiment

Collection of urine, feces and cage washings

Excreta were collected at 24 hr. intervals for 7 days. At the end of this period, the metabolism cages were washed with methanol/water (1:1) which was retained for analysis.

Retention of tissue samples

In addition to blood, samples of bone, brain, abdominal fat, gonads, heart, kidney, lung, liver, muscle and spleen were removed and retained at -20°C for subsequent analysis.

Whole body autoradiography and expired $^{14}CO_2$

One male and one female rat were orally dosed with ^{14}C alcohol labeled PP993 (4 ml/kg: Dose solution 3). Urine, feces and expired air were collected for 48 hrs. At 48 hrs. post-dosing, the rats were sacrificed, frozen and longitudinal sagital sections were cut. These sections were freeze-dried for 48 hrs. before apposition autoradiographs were prepared.

Preparation of Samples for Liquid Scintillation Counting

The preparation of urine, cagewash, feces, liver, kidney, fat, carcasses, expired air and blood for liquid scintillation counting is described in detail on appended pages 1 and 2.

Results

Excretion

Excretion data are included on appended pages 3,4,and 5. Male and female rats given a single oral dose of acid-labeled ^{14}C PP993 (1 mg/kg) excreted the major fraction of radioactivity during the 48 hrs. following administration while peak levels were detected in both urine and feces after the first 24 hrs. Total excretion levels (% of dose) at 7 days post-dosing were higher in the feces of males than females (67 vs. 54%), whereas, the opposite was observed in urine (males=20%; females=33%). The excretion rates were similar following a single oral dose of alcohol-labeled ^{14}C PP993 (1 mg/kg) and although fecal levels were higher in males and urine levels were higher in females, the differences were not as great as those observed after the administration of acid-labeled ^{14}C PP993(feces:males=63%, females=59%; urine: males=25%, females=30%).

The rate and pattern of radioactivity excretion following the administration of ^{14}C alcohol-labeled PP993 to 1 male and one female rat in the whole body autoradiography study were similar to that observed in the balance study. The levels of $^{14}CO_2$ detected 48 hrs. post-dosing were only 0.16 and 0.31% of the administered dose in the male and female, respectively.

Whole Body Autoradiography

The results of this study are presented in appended page 6. A comparison of the intensity of the label in different tissues shows that the highest amounts were detected in the nonglandular region of the stomach, stomach contents, small intestine (greatest density detected), large intestine and liver while a lower amount was detected in kidney.

Tissue Retention

Since the investigator found little or no label associated with bone, spleen, heart, gonads, lungs, or brain at 48 hrs. in the whole body autoradiography study, these tissues were not examined for residual radioactivity content at 168 hrs. after dosing. Residual radioactivity levels in liver, kidney, carcass, blood and abdominal fat, following the administration of ^{14}C acid- or ^{14}C alcohol-labeled PP993, are presented in appended pages 7 & 8. Blood levels were typically less than 0.005 ug/g tissue equivalents following administration of ^{14}C acid-or alcohol-labeled PP993. The levels of radioactivity in the liver were typically higher in males than in females, regardless of the moiety that was labeled. The levels in male liver ranged from <0.1 to 1.21% of the administered dose. Kidney levels were comparable between sexes regardless of the position of the label. These levels were slightly higher among animals receiving the alcohol label but the highest level observed was only 0.03% of the given dose. Carcass levels, which were slightly higher among animals dosed with the alcohol label, were higher in females than in males regardless of the label position. The level among females receiving the alcohol label were 2-3% of the given dose. Abdominal fat levels, expressed as ug/g tissue PP993 equivalents, were low among all animals, but were slightly higher among females than males, especially those females receiving the acid label.

Discussion

The data in this study showed that the major proportion (49-60%) of the administered ^{14}C PP993 (1 mg/kg) was excreted in the feces of rats within 48 hrs. of administration. However, depending on the sex of the rat and the position of the label, mean levels of 20-33% of the given dose were measured in urine during the 7-day observation period, which indicates that at least the levels detected in urine were absorbed. A whole body autoradiography assay revealed that the density of the labeled compound was most prevalent in the GI tract but was also readily detectable in liver and, to a lesser extent in kidney. Tissue retention assays verified the presence of residual radioactivity in liver and kidney, however, the levels were typically less than 1.0 and 0.02% , respectively, of the administered dose.

Pages 5-12 Access to FIFRA Registration Data is restricted under FIFRA section 10(g)

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PC Code:	**128912**
HED File Code	**13000 Tox Reviews**
Memo Date:	**06/12/87 12:00:00 AM**
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